REMARKS

This Amendment, filed in reply to the Office Action dated September 17, 2008, is believed to be fully responsive to each point of objection and rejection raised therein. Accordingly, favorable reconsideration on the merits is respectfully requested.

Claims 13-17 and 19 are rejected. Claims 18 and 20-29 are withdrawn from consideration. Claim 13 is amended herewith to recite that the claimed *A. pleuropneumoniae* (*App*) strain comprises "at least one mutation in a transmembrane domain-encoding segment of the *apx*IA gene, and optionally at least one mutation in a transmembrane domain-encoding segment of the *apx*IIA gene, wherein the transmembrane domain-encoding segment in each *apx*IA gene and *apx*IIA gene corresponds either to nucleotides 886 to 945, to nucleotides 697 to 759, or to nucleotides 1105 to 1215." Support for this amendment can be found throughout the specification as originally filed, such as, for example, page 3, lines 24-26, and page 10, lines 4-28. Claim 24 is amended herewith to recite a process for the production of the product of Claim 1, and thus rejoinder of withdrawn process Claims 24-29 is respectfully requested.

No new matter is added by way of this amendment. Entry and consideration of this amendment are respectfully requested.

Election/Restrictions

On page 2 of the Office Action, the Examiner maintains that Reimer *et al.* "disclose a mutant strain which comprises a mutation in at least one region of [an] A gene for *apx*I and *apx*II."

Nevertheless, the Examiner asserts that even if such is not the case, the inventions of Groups I-IV lack unity of invention because each of Groups I-IV possesses a special technical

feature "that is not required for the other groups." Specifically, the Examiner contends that a special technical feature of Group I is a strain of *Actinobacillus pleoropneumoniae* [sic.] APP, a special technical feature of Group II is a strain of *Actinobacillus pleoropneumoniae* [sic.] CECT 5985, a special technical feature of Group III is a strain of *Actinobacillus pleoropneumoniae* [sic.] CECT 5994, and a special technical feature of Group IV is a method of obtaining an organism.

Applicants disagree, respectfully, on both points.

First, Reimer *et al.* clearly do not disclose a mutant strain which comprises a mutation in at least one region of an *apx*IA and *apx*IIA gene, much less within a transmembrane domain of such, as is the special technical feature linking the claims of Groups I-IV.

As discussed previously, Reimer *et al.* disclose a ***wild-type*** strain (J45) which synthesizes and secretes exotoxins ApxI and ApxII, a mutant with the C, B, A, and D genes (*apx*ICABD operon) of ApxI ***completely deleted*** (mIT4-H), a mutant in which the ***deleted apxICABD operon is restored*** (MIT4-H/pJFF800), and a mutant in which the ***B and D genes (apxIBD operon) for ApxI are restored***. None of the aforementioned strains is immunogenic and non-haemolytic (avirulent), as claimed, because strains J45 and miT4-H/pjFF800 have the whole genetic information and are *virulent* strains, strain mIT4-H is a *non-immunogenic* and avirulent chemical mutant, and strain mIT4-H/pJFF801 has genetic modifications and is *non-immunogenic* and virulent. Thus, as would be appreciated by those of skill in the art, the special technical feature linking Groups I-IV, namely the presence of at least one mutation in a transmembrane domain-encoding segment of the *apx*IA gene, and optionally at least one mutation in a transmembrane domain-encoding segment of the *apx*IIA gene, is not disclosed, nor even remotely contemplated by Reimer *et al.* For this reason alone, Restriction is improper.

Second, the Examiner appears to believe that unity of invention is negated by the alleged presence of additional special technical features, in addition to the special technical feature linking these groups. In this regard, the Examiner appears to assert that the strains of Groups I-IV are special technical features in themselves. However, the Examiner is respectfully reminded that unity of invention exists where the Groups share ***one or more*** special technical features, that is, the technical feature that defines a contribution which each of the claimed inventions makes over the prior art. As discussed above, Groups I-IV share at least one special technical feature, *i.e.*, the presence of at least one mutation in a transmembrane domain-encoding segment of the *apx*IA gene, and optionally at least one mutation in a transmembrane domain-encoding segment of the *apx*IIA gene. Thus, unity of invention is satisfied irrespective of the Examiner's allegation that the strains themselves are a special technical feature, or that "a method of obtaining an organism" is a special technical feature. Further, Applicants note that the process claims of Group IV as amended are commensurate with the product of Group I, and thus should be rejoined as a matter of right.

Examination of all of Claims 13-23, and rejoinder of Claims 24-29 is therefore respectfully requested. Although Claim 18 remains withdrawn, Applicants note that Claim 18 is directed to the same invention as, and is further limiting of, Claim 17, currently under examination. Thus, withdrawal of this claim is also improper. Claim 18 should be examined, and such is respectfully requested.

Withdrawn Objections/Rejections

Applicants thank the Examiner for withdrawal of the objection to the specification set forth in the Office Action mailed February 13, 2008.

Applicants also thank the Examiner for withdrawal of the rejection of Claims 13-17 under 35 U.S.C. § 101 set forth in the Office Action mailed February 13, 2008, and for withdrawal of the rejection of Claim 19 under 35 U.S.C. § 112, first paragraph, set forth in the Office Action mailed February 13, 2008.

Claims 13-17 and 19 are Patentable Under 35 U.S.C. § 102(b)

1. On page 3 of the Office Action, the rejection of Claims 13-17 and 19 under 35 U.S.C. § 102(b) as allegedly being anticipated by MacInnes *et al.* (U.S. Patent No. 6,019,984), is maintained.

In maintaining the rejection, the Examiner alleges that MacInnes *et al.* disclose immunogenic, non-hemolytic *Actinobacillus pleuropneumoniae* strains comprising a mutation in at least one region of the *apx*I**A** gene and optionally a mutation in at least one region of the *apx*II**A** gene, citing the Abstract, claims, and columns 1-4. The Examiner also appears to allege that MacInnes *et al.* disclose deletion mutations of *apx*I**A** and *apx*II**A**, citing Claims 6-12, columns 3 and 4, and the figures of MacInnes *et al.*

With specific regard to Claim 19, the Examiner takes the position that the claimed product of instant Claim 19, and the product of MacInnes *et al.* are indistinguishable, citing columns 13 and 14 in support of such an assertion. Regarding Claim 16, the Examiner acknowledges that the subject matter of this claim is not expressly disclosed by MacInnes *et al.* However, the Examiner contends that such a mutation would be *inherent* in the full sequence of *apx*I**A**, allegedly disclosed by MacInnes *et al.*

Applicants strongly, but respectfully disagree with the rejection, and traverse in view of the following remarks.

To maintain a finding of anticipation, each and every element as set forth in the claim must be found, either expressly or inherently described, in a single prior art reference. See *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir 1987). For the following reasons, MacInnes *et al.* do not disclose each and every element of the claims, either expressly *or* inherently, and thus cannot anticipate the instantly claimed invention.

First, the Examiner appears to believe that MacInnes *et al.* disclose immunogenic, non-hemolytic *Actinobacillus pleuropneumoniae* strains comprising a mutation in at least one region of the *apx*I**A** gene and optionally a mutation in at least one region of the *apx*II**A** gene, citing the Abstract, claims, and columns 1-4 in support of such a contention. MacInnes *et al.* is also alleged to disclose deletion mutations of *apx*I**A** and *apx*II**A**, citing Claims 6-12, columns 3 and 4, and the figures of MacInnes *et al.* However, neither the portions of MacInnes *et al.* cited in the rejection, nor any other portion of MacInnes *et al.* for that matter, discloses an *Actinobacillus pleuropneumoniae* strain comprising a mutation in a transmembrane domain-encoding segment of the *apx*I**A** gene, and optionally a mutation in a transmembrane domain-encoding segment of the *apx*II**A** gene, either explicitly, or inherently, much less that the transmembrane domain-encoding segment of *apx*IA and *apx*IIA corresponds either to nucleotides 886 to 945, to nucleotides 697 to 759, or to nucleotides 1105 to 1215, as currently claimed.

The Abstract, claims, and columns 1-4, which are alleged to disclose as such, merely discuss different RTX toxins, which include ApxI, ApxII and ApxIII, and contemplate the modification of *Actinobacillus pleuropneumoniae* strains to produce RTX toxins which are "substantially cell-associated." Although strains are contemplated in which ApxI and ApxII are substantially cell-associated, such strains are not expressly described by MacInnes *et al.* as

having a mutation in at least one region of a transmembrane domain-encoding segment of the *apx*IA gene, and optionally a mutation in at least one region of a transmembrane domain-encoding segment of the *apx*IIA gene, nor is such an inherent property of strains in which ApxI and ApxII are substantially cell-associated. Indeed, in column 10, lines 39-43, MacInnes *et al.* disclose that one exemplary method for making an RTX toxin "cell-associated" is by using "a substance which may interfere with the secretion of an RTX toxin[, one example being] a nucleic acid sequence encoding the D and/or B transport genes inverted relative to their normal orientation for transcription i.e. antisense D and B nucleic acid molecules." (Emphasis added.) In addition, in column 11, lines 3-5, MacInnes *et al.* disclose that another exemplary method is "by targeted gene mutagenesis using allelic replacement, insertional activation, or deletion formation of the D and/or B transport genes." (Emphasis added). Thus, as would be readily understood by those of skill in the art, the modifications to the *Actinobacillus pleuropneumoniae* strains to produce ApxI toxins which are "substantially cell-associated," contemplated by MacInnes *et al.*, involve modification of the *apx*I**B** and *apx*I**D** genes, **not** *apx*I**A**, as currently claimed. Such is not a trivial difference, because as discussed in column 6, lines 26-36 of MacInnes *et al.*, and in Applicants' previous remarks, RTX toxins are encoded by four different genes, namely the A, B, C and D genes (*i.e.*, *apx*I**A**, *apx*I**B**, *apx*I**C**, *apx*I**D**). Further, in this section, MacInnes *et al.* disclose that "[t]he [RTX toxin] operon generally consists of the following four genes: an activator gene (designated "C"), a structural toxin gene (designated "A"), and two secretion genes (designated "BD")." MacInnes *et al.* simply do not teach mutating a transmembrane domain in either *apx*I**A** or *apx*II**A**, either expressly or inherently.

Further, in response to Applicants' previous arguments, the Examiner appears to assert that MacInnes *et al.* disclose the claimed invention in "transposon mutants of different strains

and APX toxins from 12 different serotypes of *Actinobacillus pleoropneumoniae* [sic.] strains," citing Figures 3 and 16-19. However, such is also incorrect. First, as discussed in column 30, lines 34-38, the transposon mutants isolated by MacInnes *et al.* "demonstrated transposon insertion in the BD region [i.e., the B and D genes]." (Emphasis added.) Clearly then, even in the transposon mutagenesis experiments, MacInnes *et al.* do not disclose an isolated immunogenic, non-haemolytic *Actinobacillus pleuropneumoniae* (*App*) strain comprising at least one mutation in a transmembrane domain-encoding segment of the *apx*IA gene, and optionally at least one mutation in a transmembrane domain-encoding segment of the *apx*IIA gene. Further, due to the unpredictability of the site of transposon insertion, it is certainly not inherent that such strains also contained a mutation in a transmembrane domain-encoding segment of the *apx*I**A** gene. Similarly, although the Examiner alleges that MacInnes *et al.* disclose that "outer membrane proteins of *Actinobacillus pleoropneumoniae* [sic.] can be altered by changing the growth conditions," such says nothing as to whether a mutation exists in a transmembrane domain-encoding segment of the *apx*IA gene.

Further still, although the Examiner appears to suggest that the instant invention is disclosed by the APX toxins shown in Figure 3, Applicants note that the only serotypes disclosed are those which produce wild-type ApxI A and C proteins, or those which do not produce any ApxI A and C proteins. The Examiner is respectfully reminded that during examination, claims are to be given their broadest reasonable construction in light of the specification as it would be interpreted by one of ordinary skill in the art. See *In re Am. Acad. Of Sci. Tech. Ctr.*, 367 F.3d 1359, 1364[, 70 USPQ2d 1827] (Fed. Cir. 2004). The serotypes which do not produce any ApxI A and C proteins are not "immunogenic" strains, as currently claimed, because ApxI (which these strains do not produce) is a critical virulence factor, and attenuated vaccines lacking ApxI

do not induce protective immune responses. See page 9, lines 8-11, and the paragraph bridging pages 2 and 3, of the specification as filed.

Thus, MacInnes *et al.* do not disclose the instantly claimed strain containing at least one mutation in a transmembrane domain-encoding segment of the *apx*IA gene, and optionally at least one mutation in a transmembrane domain-encoding segment of the *apx*IIA gene, either expressly or inherently, as is required to maintain the rejection.

Thus, MacInnes *et al.* fail to teach each and every element of the claims, and therefore cannot anticipate the claimed invention.

Withdrawal of the rejection is respectfully requested.

2. On page 4 of the Office Action, the rejection of Claims 13, 14, 15, 17 and 19 under 35 U.S.C. § 102 (b) as allegedly being anticipated by Prideaux *et al.* (U.S. Patent No. 6, 0472,183), is maintained.

In maintaining the rejection, the Examiner alleges that Prideaux *et al.* disclose immunogenic, non-hemolytic *Actinobacillus pleuropneumoniae* strains comprising a mutation in at least one region of the *apx*IA gene and optionally a mutation in at least one region of the *apx*IIA gene, citing the Abstract, claims, and columns 1-2. The Examiner further asserts that Prideaux *et al.* disclose deletion mutations of ApxIA and ApxIIA, citing Claims 1-4 and columns 3 and 4. In response to Applicants' previous argument that Prideaux *et al.* do not disclose at least one mutation in the transmembrane domain of the A gene of *apx*I, or optionally *apx*II, the Examiner cites to Example 4 and column 14 of Prideaux *et al.*, which allegedly discloses an embodiment wherein the *apx*IA gene and a kanamycin resistance gene are linked to a T5

promoter, which resulted in transformants which were kanamycin resistant and produced white colonies.

Applicants strongly, but respectfully, disagree with the rejection, and traverse in view of the following remarks.

First, Applicants again note that to maintain a finding of anticipation, each and every element as set forth in the claim must be found, either expressly or inherently described, in a single prior art reference. See *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir 1987).

Although the Examiner maintains the rejection, asserting that Prideaux *et al.* disclose immunogenic, non-hemolytic *Actinobacillus pleuropneumoniae* strains comprising a mutation in at least one region of the *apx*IA gene and optionally a mutation in at least one region of the *apx*IIA gene, citing the Abstract, claims, and columns 1-2, and that Prideaux *et al.* disclose deletion mutations of ApxIA and ApxIIA, citing Claims 1-4 and columns 3 and 4, the Examiner is respectfully requested to note that the claims as examined recited that the mutation occurs within a transmembrane domain of ApxIA, and optionally ApxIIA. Pursuant to M.P.E.P. § 2143.03, "[a]ll words in a claim must be considered in judging the patentability of that claim against the prior art." Neither in the portions of Prideaux *et al.* relied upon to support the rejection, namely the Abstract, Claims 1-4, columns 1-4, or in any other portion of Prideaux *et al.* for that matter, is the claimed strain containing a mutation in a transmembrane domain disclosed, expressly or inherently. Further, Applicants note that Claim 1 as amended recites that the transmembrane domain-encoding domain of *apx*IA and *apx*IIA corresponds either to nucleotides 886 to 945, to nucleotides 697 to 759, or to nucleotides 1105 to 1215. A strain

containing a mutation within this region of the *apx*IA, and optionally in this region of the *apx*IIA gene, is not disclosed by Prideaux *et al.*, expressly or inherently.

Further, although the Examiner cites to Example 4 and column 14 to disclose a strain containing a mutation within a transmembrane domain of ApxIA, and optionally ApxIIA, such does not disclose Applicants' claimed invention. Rather, in Example 4, Prideaux *et al.* merely disclose construction of an expression vector expressing an unmutated *apx*IA gene, which expression plasmid also contains a kanamycin resistance gene. That is, the *apx*IA gene is not even mutated, much less contain a specific mutation in a transmembrane domain that corresponds to nucleotides 886 to 945, nucleotides 697 to 759, or nucleotides 1105 to 1215 of the *apx*IA gene, as claimed. Furthermore, the Examiner supports the rejection by stating that such a construct resulted in transformants which were kanamycin resistant and produced white colonies. However, such is irrelevant. As discussed in Example 4, "[t]he SalI fragment was isolated and ligated with plG3B, which had been previously digested with SalI, and transformed into *E. Coli*." Thus, the transformants were *Escherichia coli* transformants expressing a wild-type *apx*IA gene. Clearly, such is not even an *Actinobacillus pleuropneumoniae* strain, much less an isolated immunogenic, non-haemolytic *Actinobacillus pleuropneumoniae* strain comprising at least one mutation in a transmembrane domain-encoding segment of the *apx*IA gene, and optionally at least one mutation in a transmembrane domain-encoding segment of the *apx*IIA gene, wherein the transmembrane domain-encoding segment in each *apx*IA gene and *apx*IIA gene corresponds either to nucleotides 886 to 945, to nucleotides 697 to 759, or to nucleotides 1105 to 1215, as currently claimed.

For the foregoing reasons, Prideaux *et al.* do not teach each and every element of the claims, as is required to maintain a finding of anticipation.

Accordingly, the rejection is improper and should be withdrawn, and such is respectfully requested.

Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

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